CLAIMS

1. A monoclonal antibody or a portion thereof, comprising a property in any of (a) to (g) below:

(a) reactive to human, mouse and rat connective tissue growth factors (CTGFs);

(b) reactive to both human and mouse CTGFs but not reactive to rat CTGF;

(c) reactive to both mouse and rat CTGFs but not reactive to human CTGF;

(d) inhibiting binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573), or the binding of mouse CTGF to said cell line 293-T;

(e) inhibiting binding of human CTGF to any cells of rat kidney-derived fibroblast cell line NRK-49F (ATCC CRL-1570), human osteosarcoma-derived cell line MG-63 (ATCC CRL-1427), or human lung-derived fibroblasts;

(f) inhibiting cell proliferation of rat kidney-derived fibroblast cell line NRK-49F (ATCC CRL-1570)induced by a stimulus with human or mouse CTGF; or,

(g) inhibiting an increase of hydroxyproline in the kidney, wherein said hydroxyproline level tends to be elevated.

2. The monoclonal antibody or a portion thereof according to claim 1, comprising a property in any of (a) to (c) below:

(a) obtainable by immunizing a mouse with human CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs;

(b) obtainable by immunizing a hamster with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs; or,

(c) obtainable by immunizing a rat with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs.

3. The monoclonal antibody or a portion thereof according to claim 1, comprising a property in any of (a) to (c) below:

(a) obtainable by immunizing a mouse with human CTGF or a portion thereof, reactive to human, mouse and rat CTGFs and inhibiting binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573);

(b) obtainable by immunizing a rat with mouse CTGF or a portion thereof, reactive to human, mouse and rat CTGFs and inhibiting binding of mouse CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573); or,

(c) obtainable by immunizing a hamster with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs and inhibiting binding of mouse CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573).

4. The monoclonal antibody or a portion thereof according to claim 1, wherein said monoclonal antibody is produced by a hybridoma identified by an international deposit accession No. FERM BP-6208.

5. The monoclonal antibody or a portion thereof according to claim 1, wherein said monoclonal antibody comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6208.

6. The monoclonal antibody or a portion thereof according to claim 1, wherein said monoclonal antibody is produced by a hybridoma identified by an international deposit accession No. FERM BP-6209.

7. The monoclonal antibody or a portion thereof according to claim 1, wherein said monoclonal antibody comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6209.

8. A human monoclonal antibody or a portion thereof, reactive to any human, mouse or rat CTGF.

9. The human monoclonal antibody or a portion thereof according to claim 8, wherein said human monoclonal antibody is reactive to human CTGF.

10. A human monoclonal antibody or a portion thereof, reactive to human CTGF and comprises a property in any of (a) to (d) below:

(a) inhibiting binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573);

(b) inhibiting binding of human CTGF to any of rat kidney-derived fibroblast cell line NRK-49F (ATCC CRL-1570), human

osteosarcoma-derived cell line MG-63 (ATCC CRL-1427), or human lung-derived fibroblasts;

(c) inhibiting the cell proliferation of rat kidney-derived fibroblast cell line NRK-49F (ATCC CRL-1570)induced by a stimulus with human or mouse CTGF; or,

(d) inhibiting an increase of hydroxyproline in kidney, wherein said hydroxyproline level tends to be elevated.

11. The human monoclonal antibody or a portion thereof according to any one of claims 8 to 10, wherein said human monoclonal antibody is derived from a non-human transgenic mammal which is capable of producing a human antibody.

12. The human monoclonal antibody or a portion thereof according to claim 11, wherein said human monoclonal antibody is obtainable by immunizing a non-human transgenic mammal which is capable of producing a human antibody, with human CTGF.

13. The human monoclonal antibody or a portion thereof according to any one of claims 8 to 12, wherein said non-human transgenic mammal is a transgenic mouse.

14. The human monoclonal antibody or a portion thereof according to any one of claims 8 to 13, wherein a V-region DNA encoding a heavy chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DP-5、DP-38、DP-65 and DP-75.

15. The human monoclonal antibody or a portion thereof according to any one of claims 8 to 13, wherein a V-region DNA encoding a light chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DPK1、DPK9、DPK12 and DPK24.

16. The human monoclonal antibody or a portion thereof according to any one of claims 8 to 15, wherein a V-region DNA encoding a heavy chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DP-5、DP-38、DP-65 and DP-75, and wherein a V-region DNA encoding a light chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DPK1、DPK9、DPK12 and DPK24.

17. The human monoclonal antibody or a portion thereof according to claim 9, wherein an amino acid sequence of a heavy chain variable region of said human monoclonal antibody comprises an amino acid sequence defined below in any of (a) to (j) below:

(a) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 6;

(b) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 6, wherein one or more amino acids are deleted, substituted, inserted or added;

(c) the amino acid positions 21 to 118 of the amino acid sequence of SEQ ID NO: 8;

(d) the amino acid positions 21 to 118 of the amino acid sequence of SEQ ID NO: 8, wherein one or more amino acids are deleted, substituted, inserted or added;

(e) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 10;

(f) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 10, wherein one or more amino acids are deleted, substituted, inserted or added;

(g) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 12;

(h) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 12, wherein one or more amino acids are deleted, substituted, inserted or added;

(i) the amino acid positions 21 to 117 of the amino acid sequence of SEQ ID NO: 14; or,

(j) the amino acid positions 21 to 117 of the amino acid sequence of SEQ ID NO: 14, wherein one or more amino acids are deleted, substituted, inserted or added.

18. The human monoclonal antibody or a portion thereof according to claim 9, wherein an amino acid sequence of a light chain variable region of said human monoclonal antibody comprises an amino acid sequence in any of (a) to (j)below:

(a) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 16;

(b) the amino acid positions 21 to 120 of the amino acid sequence

of SEQ ID NO: 16, wherein one or more amino acids are deleted, substituted, inserted or added;

(c) the amino acid positions 21 to 121 of the amino acid sequence of SEQ ID NO: 18;

(d) the amino acid positions 21 to 121 of the amino acid sequence of SEQ ID NO: 18, wherein one or more amino acids are deleted, substituted, inserted or added;

(e) the amino acid positions 23 to 117 of the amino acid sequence of SEQ ID NO: 20;

(f) the amino acid positions 23 to 117 of the amino acid sequence of SEQ ID NO: 20, wherein one or more amino acids are deleted, substituted, inserted or added;

(g) the amino acid positions 17 to 111 of the amino acid sequence of SEQ ID NO: 22;

(h) the amino acid positions 17 to 111 of the amino acid sequence of SEQ ID NO: 22, wherein one or more amino acids are deleted, substituted, inserted or added;

(i) the amino acid positions 23 to 118 of the amino acid sequence of SEQ ID NO: 24; or,

(j) the amino acid positions 23 to 118 of the amino acid sequence of SEQ ID NO: 24, wherein one or more amino acids are deleted, substituted, inserted or added.

19. A monoclonal antibody or a portion thereof, reactive to human CTGF, which is produced by a hybridoma identified by an international deposit accession No. FERM BP-6535.

20. A monoclonal antibody or a portion thereof, reactive to human CTGF and comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6535.

21. A monoclonal antibody or a portion thereof, reactive to human CTGF, which is produced by a hybridoma identified by an international deposit accession No. FERM BP-6598.

22. A monoclonal antibody or a portion thereof, reactive to human CTGF and comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6598.

23. A monoclonal antibody or a portion thereof, reactive to human CTGF, which is produced by a hybridoma identified by an international deposit accession No. FERM BP-6599.

24. A monoclonal antibody or a portion thereof, reactive to human CTGF and comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6599.

25. A monoclonal antibody or a portion thereof, reactive to human CTGF, which is produced by a hybridoma identified by an international deposit accession No. FERM BP-6600.

26. A monoclonal antibody or a portion thereof, reactive to human CTGF and comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6600.

27. A monoclonal antibody or a portion thereof, reactive to human CTGF, and which is non-reactive to an antigen-antibody complex of human CTGF and the monoclonal antibody reactive to human CTGF of claim 17 or 18.

28. The monoclonal antibody or a portion thereof according to claim 27, wherein said monoclonal antibody is a human monoclonal antibody.

29. A monoclonal antibody or a portion thereof, reactive to rat CTGF.

30. A recombinant chimeric monoclonal antibody, reactive to human CTGF, and of which a variable region is derived from a variable region of the monoclonal antibody according to any one of claims 2 to 7, 27 or 29 and of which a constant region is derived from a constant region of a human immunoglobulin.

31. A recombinant humanized monoclonal antibody, reactive to human CTGF, of which a whole or portion of the complementarity-determining regions of a hyper-variable region is derived from complementarity-determining regions of the monoclonal antibody of any one of claims 2 to 7, 27 or 29, of which framework regions of a hyper-variable region are derived from the framework regions of a human immunoglobulin and of which a constant region is derived from a constant region of a human immunoglobulin.

32. A cell producing the monoclonal antibody according to any one of claims 1 to 29.

33. A cell producing the recombinant monoclonal antibody according to claim 30 or 31.

34. The cell according to claim 32, wherein said cell is a hybridoma obtainable by fusing a mammalian myeloma cell with a mammalian B cell which is capable of producing the monoclonal antibody.

35. The cell according to claim 32 or 33, wherein said cell is a genetically engineered cell transformed by either one or both of the DNAs encoding a heavy chain and light chain of the monoclonal antibody.

36. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6535.

37. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6598.

38. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6599.

39. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6600.

40. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6208.

41. The hybridoma according to claim 34, wherein said hybridoma is identified by an international deposit accession No. FERM BP-6209.

42. An antibody-immobilized insoluble carrier on which the monoclonal antibody according to any one of claims 1 to 31 is immobilized.

43. The antibody-immobilized insoluble carrier according to 42, wherein said insoluble carrier is selected from the group consisting of plates, test tubes, tubes, beads, balls, filters and

membranes.

44. The antibody-immobilized insoluble carrier according to 42, wherein said insoluble carrier is a filter or membrane, or that used for affinity column chromatography.

45. A labeled antibody which is prepared by labeling the monoclonal antibody of any one of claims 1 to 31 with a labeling agent capable of providing a detectable signal by itself or together with other substances.

46. The labeled antibody according to claim 45, wherein said labeling agent is an enzyme, fluorescent substance, chemiluminescent substance, biotin, avidin, or radioisotope.

47. A kit for detecting or assaying mammalian CTGF, comprising at least one monoclonal antibody, an antibody-immobilized insoluble carrier, and a labeled antibody, which is selected from the group consisting of the monoclonal antibody according to any one of claims 1 to 31, the antibody-immobilized insoluble carrier according to claim 42 or 43, and the labeled antibody according to claim 45 or 46.

48. The kit for detecting or assaying mammalian CTGF according to claim 47, comprising the antibody-immobilized insoluble carrier according to claim 42 or 43 and the labeled antibody according to claim 45 or 46.

49. A method for detecting or assaying mammalian CTGF by an immunoassay using at least one monoclonal antibody, an antibody-immobilized insoluble carrier, and a labeled antibody, which is selected from the group consisting of the monoclonal antibody according to any one of claims 1 to 31, the antibody-immobilized insoluble carrier according to claim 42 or 43, and the labeled antibody according to claim 45 or 46.

50. The method for detecting or assaying mammalian CTGF by an immunoassay according to claim 49, comprising at least the following steps of (a) and (b):

(a) reacting a sample with the antibody-immobilized insoluble carrier according to claim 42 or 43; and,

(b) reacting the labeled antibody according to claim 45 or 46 with an antigen-antibody complex formed by binding mammalian CTGF

in said sample to the antibody-immobilized insoluble carrier.

51. The method for detecting or assaying mammalian CTGF by an immunoassay according to claim 49, comprising at least the following steps of (a) and (b):

(a) reacting a sample with the labeled antibody according to claim 45 or 46; and,

(b) reacting the antibody-immobilized insoluble carrier according to claim 42 or 43 with the antigen-antibody complex formed by binding said labeled antibody and mammalian CTGF in said sample.

52. The method for detecting or assaying mammalian CTGF by an immunoassay according to claim 49, comprising at least the following step of (a):

(a) reacting a mixture comprising the antibody-immobilized insoluble carrier according to claim 42 or 43, the labeled antibody according to claim 45 or 46, and a sample.

53. The method for detecting or assaying mammalian CTGF by an immunoassay according to claim 49, comprising at least the following step of (a):

(a) reacting a sample and a mammalian CTGF standard labeled with a labeling agent capable of providing a detectable signal by itself or together with other substances, with the antibody-immobilized insoluble carrier according to claim 42 or 43.

54. The method for detecting or assaying mammalian CTGFs by an immunoassay according to claim 49, comprising at least the following steps of (a) and (b):

(a) reacting the monoclonal antibody according to any one of claims 1 to 31 with a mixture comprising a sample and a mammalian CTGF standard labeled with a labeling agent capable of proving a detectable signal by itself or together with other substances; and,

(b) reacting a mammalian antiserum reactive to said monoclonal antibody with the antigen-antibody complex formed by binding mammalian CTGF in said sample or said labeled mammalian CTGF standard and said monoclonal antibody.

55. The method for detecting or assaying mammalian CTGFs by an immunoassay according to claim 49, comprising at least the following steps of any of (a) to (c):

(a) reacting the monoclonal antibody according to any of one claims 1 to 31 with a sample;

(b) reacting a mammalian CTGF standard labeled with a labeling agent capable of providing a detectable signal by itself or together with other substances with a reaction product resulted from the reaction in step (a); and,

(c) reacting a mammalian antiserum reactive to said monoclonal antibody with the antigen-antibody complex formed by binding mammalian CTGF in said sample or said labeled mammalian CTGF standard, and said monoclonal antibody.

56. A kit for separating or purifying mammalian CTGF, comprising the antibody-immobilized insoluble carrier according to claim 42 or 44.

57. A method for separating or purifying mammalian CTGF, comprising using affinity chromatography with the antibody-immobilized insoluble carrier according to claim 42 or 44.

58. The purification method for mammalian CTGF according to claim 57, wherein said affinity chromatography is affinity column chromatography.

59. A transgenic mouse in which DNA encoding human CTGF is integrated into an endogenous gene locus.

60. A rat CTGF comprising an amino acid sequence of, or substantially equivalent to an amino acid sequence of SEQ ID NO: 2.

61. A DNA encoding a rat CTGF comprising the amino acid sequence of SEQ ID NO: 2.

62. The DNA according to claim 61, comprising nucleotide sequence in the positions of 213 to 1256 of SEQ ID NO: 1.

63. A pharmaceutical composition comprising the monoclonal antibody or a portion thereof according to any one of claims 2 to 31 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising the human monoclonal antibody or a portion thereof according to any one of claims 9 to 18 or 28 and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising the human monoclonal antibody or a portion thereof according to any one of claims 14 to 18 and 28.

66. The pharmaceutical composition according to any one of claims 63 to 65, for inhibiting proliferation of cells capable of proliferating by a stimulus with CTGF.

67. The pharmaceutical composition according to any one of claims 63 to 65, for treating or preventing a disease accompanied by proliferation of cells capable of proliferating by a stimulus with CTGF;

68. The pharmaceutical composition according to claim 66 or 67, wherein said proliferation is cell proliferation in a tissue selected from the group consisting of brain, neck, lung, heart, liver, pancreas, kidney, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue and blood vessels.

69. The pharmaceutical composition according to claim 68, wherein said tissue is lung, liver, kidney or skin.

70. The pharmaceutical composition according to claim 69, wherein said tissue is the kidney.

71. The pharmaceutical composition according to claim 67, wherein said disease is further accompanied by tissue fibrosis.

72. The pharmaceutical composition according to claim 71, wherein said tissue fibrosis is tissue fibrosis in lung, liver, kidney or skin.

73. The pharmaceutical composition according to claim 72, wherein said tissue fibrosis is kidney fibrosis.

74. A pharmaceutical composition for treating or preventing a kidney disease, comprising a CTGF inhibitor or an agent for inhibiting CTGF production, and a pharmaceutically acceptable carrier.

75. The pharmaceutical composition according to claim 74, wherein said inhibitor is a monoclonal antibody reactive to CTGF.

76. The pharmaceutical composition according to claim 74, wherein said inhibitor is the monoclonal antibody of any one of claims 9 to 31.

77. The pharmaceutical composition according to 76, wherein said inhibitor is the human monoclonal antibody according to any one of claims 14 to 18 and 28.

78. The pharmaceutical composition according to any one of claims 74 to 77, wherein said disease is accompanied by tissue fibrosis.

79. A pharmaceutical composition for inhibiting proliferation of cells in kidney which are capable of proliferating by a stimulus with CTGF, comprising a substance having an activity of inhibiting proliferation of said cells and a pharmaceutically acceptable carrier.

80. The pharmaceutical composition according to claim 79, wherein said substance is a monoclonal antibody reactive to CTGF.

81. The pharmaceutical composition according to claim 79, wherein said inhibitor is the monoclonal antibody according to any one of claims 9 to 31.

82. The pharmaceutical composition according to claim 81, wherein said inhibitor is the human monoclonal antibody according to any one of claims 14 to 18 and 28.

add B1

Add C5